Anti-microbial Resistance In Atopic Dermatitis: Need for an Urgent Rethink

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Abbreviations: SA- *Staphylococcus aureus*, AD- atopic dermatitis; AMR- antimicrobial resistance; MRSA- methicillin resistant *Staphylococcus aureus*; MSSA- methicillin sensitive *Staphylococcus aureus*; FA- fusidic acid; MupR- mupirocin resistant; ST- sequence type

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Introduction

Atopic dermatitis (AD) results from a complex interplay of host genetic and environmental factors. There is a long established association between AD and *Staphylococcus aureus*. In healthy individuals this organism has a dichotomous relationship with the host, being a frequent component of the human microbiome, carried asymptomatically, and on occasion, an opportunistic pathogen capable of causing or influencing a broad ranging disease. In AD, high carriage rates of *S. aureus* on affected skin is commonly observed, with recent meta-analysis evidence demonstrating colonisation in approximately 70% of affected individuals [1]. High frequency of carriage, and a high colonization burden, have been linked with disease severity in AD. Despite this association, relatively modest advances have been made in understanding if this is causal or consequential. With increasing numbers of microbiome studies it is becoming evident that wider cutaneous microbial imbalances, or dysbiosis, likely contribute to the observed abundance of *S. aureus* seen in AD, as well as the aetiology of AD. In contrast, antimicrobials, which cause dysbiosis by virtue of their activity, are still used routinely to target *S. aureus* in the management of this condition. Important questions remain about the extent to which microbiome composition is important in determining the ability of *S. aureus* to thrive and to drive disease, and the extent to which therapeutic use of antimicrobials may impact on the microbiome and the *S. aureus* population within it. Against a backdrop of increasing levels of antimicrobial resistance (AMR), careful stewardship of antibiotics is vital to maintain their therapeutic efficacy. In AD, this is of particular concern as *S. aureus* is an organism that is adept at developing AMR, and also due to the collateral damage that antibiotics inflict on the microbiome.

The concept of AD as a microbial diathesis has been a subject of detailed study over the past decade, especially with the advent of 16S rRNA sequencing as a tool to better describe the diversity of the cutaneous bacterial microbiome. Alterations in microbiome composition have been shown to vary in affected individuals compared to healthy controls. People with established AD have overall reduced cutaneous bacterial diversity in comparison to healthy individuals [2]. Specific signature shifts of populations are observed to occur during disease exacerbation, mirroring increasing disease severity, with expansion of staphylococcal populations, primarily *S. aureus* and *S. epidermidis* [2]. Development of AD may also be influenced by microbiome composition during infancy, with commensal staphylococci having a protective effect and being significantly less abundant in children who go on to develop AD by 12 months [3]. Presently *S. aureus* remains the dominant organism in terms of potential contribution to AD pathogenesis. The involvement of *S. aureus* in disease activity is almost certainly multi-modal, through pro-inflammatory interaction by adherence to keratinocytes to secretion of toxins and proteases, reviewed in detail[4], and illustrated in Figure 1. At the genetic level, evidence of *S. aureus* strain association with AD is accumulating. Specific clones of *S. aureus* are more frequently isolated from diseased skin, than other more widely circulating clones in the general population. This suggests that there may be specific, clonally-associated, properties allowing it to preferentially survive on atopic skin, and drive the pathology of AD[5,6].

Therapeutic interventions in AD are directed at alleviating disease severity through moisturisation, resolving inflammation, and reducing bacterial burden, all of which may indirectly influence the microbiome. Emollients are the foundation of management in AD, improving epidermal barrier function, with usage reducing AD severity. Daily emollient usage in

high-risk infants may prevent the onset of AD. Recent analysis has revealed that as skin pH decreases with improved barrier function, in moisturiser treated infants, cutaneous bacterial diversity recovers, with specific higher abundance of *Streptococcus salivarius* in individuals who did not develop AD [7]. Topical corticosteroids are hypothesised to have a similar influence, through their anti-inflammatory as well as barrier altering effects, but this remains to be properly characterised.

Antimicrobials are another pillar of AD treatment, which include topical and oral antibiotics, antiseptic containing soap substitutes, and bleach baths. The precise impact they have on the AD microbiome is unclear, as they are generally used in combination with steroids and emollients, making it difficult to attribute microbiome changes to any one of these individual measures. Characterisation of cutaneous microbiota during and post treatment, both with 16S rRNA or metagenomics approaches, does not allow for resolution beyond species level, meaning variability within specific species at strain level, such as acquisition of a resistance gene, is not possible to determine. Deep sequencing of colonies isolated from skin swabs has provided a higher resolution to investigate *S. aureus* populations from AD patients. Within patients there is evidence of clonal expansion and diversification of the *S. aureus* population, and moreover, genetic adaptation to therapeutic interventions [8]. These culture-based studies have also almost uniformly focused on *S. aureus*, therefore the impact on the remainder of the microbiota remains unresolved.

Given fluctuations in *S. aureus* burden, which correlate with AD severity, antimicrobials are frequently used to target this pathogen. Primarily they are used as anti-staphylococcal agents, to

reduce the burden of the organism and its pro-inflammatory effect. Despite lack of robust evidence to support this practice [9], most dermatologists, allergists and other healthcare providers do so because of a perceived clinical benefit. In milder disease, more frequently seen by non-specialists, antibiotic therapy has no benefit over emollients and appropriate strength topical corticosteroids [10]. One potential downside in changing this practice in individuals with greater disease severity is that this patient group is at significantly higher risk of invasive *S. aureus* infection [11]. Withholding antibiotics in people with more severe AD during disease flares with clinical evidence of infection is therefore clinically difficult to justify, and warrants study to determine if they do indeed improve clinical outcomes when used for severe flares. A confounding and critical issue in this is the lack of universally accepted definitions of colonization versus infection amongst health care providers leading to widely differing thresholds for antibiotic use and indeed overuse.

Aside from the uncertain benefits of using antimicrobial agents for the management of AD it is important to consider the wider impact of these agents on *S. aureus* populations associated with AD. Genomic studies have illustrated the role that extensive use of antibiotics has had in generating and maintaining AMR in pathogen populations. The recent history of *S. aureus* as a pathogen is punctuated by the emergence and spread of AMR clones. The introduction of new antibiotics has invariably been followed shortly after by the appearance of resistant variants in clinical practice; the genetic mechanisms underpinning this resistance are summarised in Figure 2. Genomic epidemiological studies have revealed how the widespread use of new antibiotics can drive the epidemic spread of emergent resistant clones [12,13]. This increasing burden of resistance therefore has specific relevance to practitioners who manage AD in the

outpatient/ambulatory setting, especially those providing care for the group of patients who more frequently receive antibiotics for chronic disease management, and who therefore are at risk of the consequences of AMR. Prescribing practices in this patient group potentially select and maintenance of problematic resistance patterns.

The impact of AMR on the management of AD is influenced by the prevalence of resistance in the general population. The most pertinent example is methicillin-resistant *S. aureus* (MRSA), where population level prevalence, particularly of community-associated MRSA (CA-MRSA), is higher in the United States compared with Northern Europe. Reported rates of MRSA in association with AD in the USA range widely from 6.8% [14] to 45%, [15] while in Europe rates are 2% or lower [16,17]. High prevalence of MRSA in AD drives more frequent use of broader spectrum agents, for instance clindamycin, which in turns drives higher rates of resistance.

Topical antibiotics pose a particular problem in terms of resistance, outlined in Figure 3. They are more widely used and are applied with a range of adherence to correct application recommendations, often with sub-therapeutic dosing. These factors likely drive rapid generation of resistance in treated individuals. In Europe, usage of topical fusidic acid (FA) has led to problematic rates of resistance specifically in dermatology, with rates of 40% or more are commonly reported in AD patients, and specific mechanisms of resistance in this population [16,17]. In contrast, FA susceptibility is almost uniform in the USA where the agent is not used. Mupirocin resistance (MupR), conversely, is more prevalent in countries with higher MRSA prevalence. Reported rates from the USA in dermatology patients range from 1.8% to 31.3%, with AD a disease-specific risk factor for carriage of MupR *S. aureus* [18]. Studies from across

Europe, where the agent is generally reserved for MRSA decolonisation therapy, report much lower ranges of MupR associated with AD between 0.7% and 4% [16,19].

Prevalence aside, there is evidence to suggest that MRSA may be associated with greater disease severity. Altered toxin secretion profiles of CA-MRSA strains is one mechanism that has been proposed as an explanation for this [20]. MRSA has a greater effect on displacing cutaneous diversity than methicillin-sensitive *S. aureus* (MSSA) during AD flares[14]. MRSA has specific effects on corynebacterial and streptococcal species and not on *Staphylococcus epidermidis*, another staphylococcal component of the skin microbiome. However, overall MRSA colonisation did not correlate with overall disease severity.[14] These are interesting observations, and both the aforementioned studies demonstrate the potential for lineage-specific properties of *S. aureus* having differing effects on the skin in AD. Methicillin resistance is restricted within specific lineages, meaning that the observed variable biological impact does not necessarily relate to resistance profile and is perhaps more reflective of the general biological properties of the MRSA clones.

Even when directly targeted, antimicrobial therapy will still have off-target effects both on the organism as well as the rest of the cutaneous microflora. This is exemplified by observations from New Zealand, which has one of the world's highest rates of usage of topical antibiotics. In this setting, combined genomic and epidemiological evidence has shown that usage of mupirocin and FA, largely for minor skin infections, led to the selection and success of a multi-drug resistant sequence type (ST) 1 *S. aureus* clone in the country [21]. The authors of this study also demonstrate that *in vitro* exposure to these agents co-selected for strains carrying completely

unrelated AMR determinants. When considering the wider impact of AMR selection and AD, it is worth reflecting on *S. epidermidis*, which is carried almost universally as a commensal and which may have modulating effects on AD development or severity and on SA carriage. Antimicrobial usage in general population terms has led to the emergence of multi-drug resistant clones of *S. epidermidis* globally, worryingly harbouring resistance to last-line glycopeptide antibiotics as well as topical agents such as FA [22]. These examples illustrate that prescribing in AD has the potential to influence wider populations of *S. aureus* but also the effect that antibiotics may have on other commensals when used in AD.

As a final point for consideration, AMR generated by classes of antibiotics used to treat AD can also directly influence virulence. Mupriocin resistance, conferred by a point mutation in the *ileS* gene, significantly reduces the production of phenol soluble modulins by *S. aureus*, including α and δ toxins [23]. This finding holds specific relevance as these toxins have been directly mechanistically linked to AD skin inflammation; meaning AMR may have pleiotropic effects on microbial association with the disease.

Looking to the future there is an urgent need to consider the impact that antimicrobials have on *S. aureus* and the wider cutaneous microbiota when used in AD. These interventions will doubtless have broader ranging consequences than we currently understand. With the emerging problem of AMR there is a need to be more critical of existing practice, and an imperative need for high quality clinical evidence to support such widespread antimicrobial interventions. There is also a need for targeted functional research to define the precise role *S. aureus* plays in AD to justify and precisely target anti-staphylococcal treatment. With dwindling antimicrobial reserves,

harnessing the potential therapeutic benefits of naturally occurring cutaneous antimicrobial peptides is an interesting prospective approach on the horizon [24], which may provide us a route to circumvent the well-recognised problems with using broad-spectrum antibiotics in AD.

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Figure Legends

Figure 1: Postulated mechanisms by which *Staphylococcus aureus* contributes to the pathophysiology of atopic dermatitis.

Figure 2: *S. aureus* resistance mechanisms

Figure 3: *S. aureus* colonizing AD affected skin